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Early hepatic signals of fat overload

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Running head: Overfeeding and hepatokines

Abbreviations

FGF21 - fibroblast growth factor 21

LECT2 - leukocyte cell-derived chemotaxin 2

Periods of overfeeding are a common occurrence in most developed countries, especially at times of celebration and festivities. When combined with reduced physical activity, overconsumption of food results in rapid changes in metabolic health, increasing blood pressure, blood glucose and cholesterol concentrations, whilst decreasing insulin sensitivity (1, 2). Some of these responses are observed as early as after one day of high-fat overfeeding (3). The liver is a key organ which orchestrates metabolism by directly contributing to the storage and processing of metabolites, in addition to secreting peptides that act as endocrine factors directing nutrient handling in peripheral tissues (4, 5).

A number of peptides have been reported to be secreted by the liver to signal energy availability. These include fibroblast growth factor 21 (FGF21) and leukocyte cell-derived chemotaxin 2 (LECT2). FGF21 is predominantly secreted by the liver in response to exercise, low-protein and ketogenic diets, fructose and ethanol ingestion (6, 7). It has also been suggested that FGF21 is a key endocrine regulator of sugar and alcohol appetite, as the rise in FGF21 in response to ingestion of fructose or ethanol may inhibit the consumption of these dietary components. FGF21 may therefore provide a negative feedback loop to attenuate excessive intakes of dietary components that could be harmful to metabolic health (7). LECT2 also seems to be elevated in situations of energy excess (8), although the time course of each of these hormones in response to specific types of energy excess in humans is unclear.

In this issue of Journal of Nutrition, Willis et al. (9) report on a study which characterized the human time course of these hepatic signals to an energy surplus induced primarily from increased dietary fat intake. A group of healthy men performed

two, 7-day dietary periods with a three-week washout, performed in a randomized order. Importantly, one of these dietary periods was a control condition, which aimed to maintain energy balance and provided ~100 g fat per day. The other dietary condition was a high-fat, high-energy diet, providing ~350 g fat per day and aiming to provide 150% of estimated daily energy requirement. FGF21 concentrations responded rapidly to high-fat overfeeding, with fasting FGF21 concentrations increasing by ~2-fold within 24 hours. FGF21 remained elevated after 3 days of overfeeding, but interestingly, returned to basal concentrations by day 7, at which point FGF21 concentrations during high-fat overfeeding were no longer different to during the control diet. LECT2 concentrations on the other hand, displayed a very different time course and quantitatively more modest response. Differences in LECT2 concentrations between diets only became apparent by day 3 of high-fat overfeeding, and the increase induced by high-fat overfeeding continued through day 7.

The report by Willis et al. provides important insights into the time course of hepatic signals of fat overload in humans. The rapid and large, but transient rise in FGF21 concentrations, in contrast to the more modest but sustained rise in LECT2 concentrations, suggest these signals are differentially regulated and could be used in combination to provide insight into the type or duration of energy stress that has been induced. With much focus on the role of (low) protein, high fructose and ethanol intakes in regulating FGF21 concentrations, the present data suggest that FGF21 is also responsive to high-fat overfeeding in humans, and may not, therefore, be a regulator of sugar and ethanol intake specifically. It is possible that the hyperinsulinemia induced by overfeeding, may have driven the increased FGF21 concentrations, as hyperinsulinemic clamps can induce FGF21 secretion in humans

under both euglycemic and hyperglycemic conditions (10). As overfeeding of any macronutrient (on a mixed-macronutrient diet) induces higher postprandial insulin responses, increased FGF21 concentrations, may have been due to postprandial hyperinsulinemia, rather than the high-fat intake *per se*. However, further work directly comparing overfeeding of carbohydrate *versus* fat would be required to better understand the regulation of FGF21 and LECT2 secretion in response to nutrient surplus.

An important factor to consider in nutrition research, especially when overfeeding is prescribed, is the interaction with physical activity. Differences in physical activity in response to overfeeding can introduce variance into the degree of energy surplus (11), and even when the energy surplus is controlled, a higher *versus* a lower energy flux can produce profoundly different metabolic responses (1). Willis et al. used objective measures to characterise physical activity during the interventions (9), which is a strength of the study, and physical activity appeared to be sustained at habitual levels. Given the potential for physical activity to alter nutrient partitioning, further work should aim to establish these hepatic signals of energy surplus under conditions of high and low-energy flux, ideally with measures of intrahepatic lipid and glycogen concentrations (*e.g.* by using Magnetic Resonance Spectroscopy) to establish links between nutrient storage and hepatokine secretion.

The work by Willis et al. (9) provides new insights into the regulation of hepatically derived hormones that signal energy surplus in humans. This lays the foundations for future work to unpick the functional relevance of the time course and magnitude of elevation of FGF21 and LECT2 in humans during high-fat overfeeding, and thus

whether these peptides can be exploited for therapeutic benefit or used as a measurement tool to characterize the type of energy stress that is imposed.

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